respectfully ask the Examiner to initial and return the 1449 Form to their undersigned representative, confirming consideration of the listed references.

II. Alleged Indefiniteness

A. Claims 1 to 12, 14 to 18, 20, 21, and 23 to 26 have been rejected under 35 U.S.C. § 112, second paragraph because the terms "heterocycloalkyl," "heterocycloalkenyl," "bicycloheteroalkyl," "bicycloheteroalkenyl," "tricycloheteroalkyl," and "tricycloheteroalkenyl," are allegedly indefinite. Applicants respectfully traverse the rejection because the terms convey a clear and definite meaning to those skilled in the art.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 [second paragraph] demands no more." *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). If a skilled artisan can determine whether a particular chemical compound is or is not within the scope of a claim, the requirement of § 112, second paragraph has been fulfilled. *In re Miller*, 441 F.2d 689, 692 (C.C.P.A. 1971).

Definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971); M.P.E.P. § 2173.02. When the present claim language is so examined, it is apparent that the meaning of the cited terms would be readily understood by those of ordinary skill in the art. The term "cycloalkyl" is defined in *Grant & Hackh's Chemical Dictionary* (excerpt attached hereto as Appendix A) as the generic name for radicals derived from

cycloalkanes. In addition, the term "heterocyclic" is defined as pertaining to dissimilar atoms ***in*** a ring. "Heterocyclic atom" is defined as any atom, other than carbon, ***in*** an atomic ring, and a "heterocyclic compound" is defined as ***a ring bearing atoms other than C in its nucleus***. Pyrrole, pyran, and thiophene are depicted as examples of heterocyclic compounds. (*Grant & Hackh's Chemical Dictionary*, Betty J. Sun and Susan Thomas, editors, McGraw-Hill, Inc., 1987, pages 167 and 282). In addition, the specification lists numerous examples of heterocycloalkyl and heterocycloalkenyl groups, such as tetrahydrofuranyl, pyrrolidinyl, oxazolidinyl, dioxolanyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, pyranyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, and oxathiazinyl. (See page 16, lines 1 to 14 of the specification as filed).

Those skilled in the art, therefore, would understand the term "heterocycloalkyl" to refer to a cycloalkyl radical containing an atom, other than a carbon atom, ***in*** the cycloalkyl ring. Similarly, those skilled in the art would also understand the terms "bicycloheteroalkyl" and "tricycloheteroalkyl" to refer to moieties containing two cycloalkyl rings and three cycloalkyl rings, respectively, in which at least one of the rings contains an atom, other than carbon, in the ring. In addition, those skilled in the art would also understand the terms "heterocycloalkenyl," "bicycloheteroalkenyl," and "tricycloheteroalkenyl" to refer to moieties containing one, two, and three cycloalkenyl groups (*i.e.*, cycloalkyl groups containing at least one double bond), respectively, in which at least one of the rings contains an atom, other than carbon, in the ring.

The specification states that the heterocycloalkyl, heterocycloalkenyl, bicycloheteroalkyl, bicycloheteroalkenyl, tricycloheteroalkyl, and tricycloheteroalkenyl groups may be ***optionally substituted***, and lists the optional substituents that may be present

on the groups. (See page 15, lines 23 to 25 and page 16, line 16 to page 17, line 5). The term "substituent" is defined in *Grant & Hackh's Chemical Dictionary* (excerpt attached hereto as Appendix A) as any atom or group replacing the hydrogen of a parent compound. (*Grant & Hackh's Chemical Dictionary*, Betty J. Sun and Susan Thomas, editors, McGraw-Hill, Inc., 1987, page 558). Those of skill in the art, therefore, understand that hydrogen atoms present on the ring atoms of the heterocycloalkyl, heterocycloalkenyl, bicycloheteroalkyl, bicycloheteroalkenyl, tricycloheteroalkyl, and tricycloheteroalkenyl groups may be replaced with the substituents listed on pages 16 and 17 of the specification.

When the claim language is examined in light of the specification and from the viewpoint of those of ordinary skill in the art, the terms "heterocycloalkyl," "heterocycloalkenyl," "bicycloheteroalkyl," "bicycloheteroalkenyl," "tricycloheteroalkyl," and "tricycloheteroalkenyl," therefore, reasonably apprise those skilled in the art of the scope of the claims. Although the Office Action questions whether the term "heterocycloalkyl" is "an alkyl substituted by a heterocycle...a cycloalkyl interrupted by a heteroatom..., or a cycloalkly substituted by a heteroatom,"[1] as discussed above, those of skill in the art understand the term to refer to a cycloalkyl interrupted by a heteroatom. Those skilled in the art understand a heterocyclic group to be a ring containing at least one atom other than carbon. (*Grant & Hackh's Chemical Dictionary*, Betty J. Sun and Susan Thomas, editors, McGraw-Hill, Inc., 1987, pages 167 and 282). Accordingly, those skilled in the art understand that a heterocycloalkyl group is a cycloalkyl ring bearing at least one ring atom other than a carbon atom, and is ***not*** an alkyl group substituted by a heterocyclic group or a cycloalkyl group substituted by a heteroatom, which those skilled in the art understand to be substituted alkyl and cycloalkyl groups, respectively.

[1] Office Action dated February 14, 2003, page 4.

Those of ordinary skill in the art would understand which groups are encompassed by the terms "heterocycloalkyl," "heterocycloalkenyl," "bicycloheteroalkyl," bicycloheteroalkenyl," "tricycloheteroalkyl," and "tricycloheteroalkenyl," and would not have any difficulty determining whether a particular compound falls within the scope of the claims. Accordingly, the requirements of the second paragraph of 35 U.S.C. § 112 have been met, and Applicants respectfully request withdrawal of the rejection.

B. Claims 25 and 26 have been rejected under 35 U.S.C. § 112, second paragraph as indefinite because it is allegedly unclear which diseases and treatments are encompassed by the claims. Without conceding the correctness of the assertion, and to advance prosecution, claims 25 and 26 have been cancelled, obviating the rejection. Accordingly, Applicants respectfully request withdrawal thereof.

III. Alleged Lack of Enablement

A. Claims 1 to 21, 23 to 26, and 27 have been rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not enable those skilled in the art to make solvates and hydrates of the claimed compounds. Without conceding the correctness of the assertion, and to advance prosecution, claims 1, 15, 16, and 19 have been amended to delete the terms "solvates" and "hydrates." The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

B. Claim 21 has been rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly fails to enable those of skill in the art to treat multiple sclerosis with the claimed α4 integrin inhibitors. Without conceding the correctness of the assertion, and to advance prosecution, claim 21 has been amended to delete "multiple sclerosis," obviating the rejection. Accordingly, Applicants respectfully request withdrawal thereof.

IV. Alleged Double Patenting

Claims 1 to 14, 20, 21, and 23 to 26 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 6, 10 to 15, and 18 to 22 of U.S. Patent No. 6,518,283. In addition, claims 1 to 21 and 23 to 27 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 14 and 18 of U.S. Patent No. 6,455,539. Without conceding the correctness of the rejections, and to advance prosecution, terminal disclaimers are being submitted herewith in which the owner of the present application disclaims the terminal part of the statutory term of any patent granted on the instant application that would extend beyond the expiration date of the full statutory term, as shortened by any terminal disclaimer, of U.S. Patent No. 6,518,283 and U.S. Patent No. 6,455,539. The obviousness-type double patenting rejections have therefore been obviated, and Applicants respectfully request withdrawal thereof.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

Date: **June 4, 2003**

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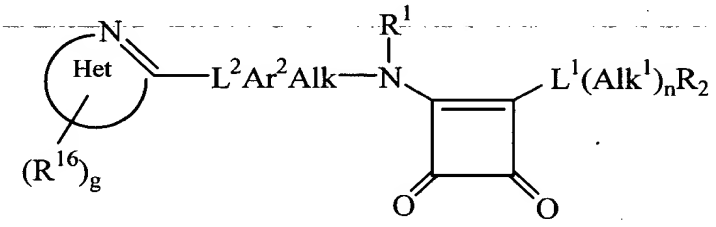
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 25 and 26 have been cancelled.

Claims 1, 15, 16, 19, and 21 have been amended as follows.

1. (Amended twice) A compound of formula (1):



(1)

wherein

Het is a bicyclic fused ring heteroaromatic group;

g is zero or the integer 1, 2, 3 or 4;

Each R^{16}, which may be the same or different, is an atom or group $-L^3(Alk^2)_tL^4(R^4)_u$,

L^3 and L^4, which may be the same or different, are each a covalent bond or a linker atom or group -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-N(R^8)O-$, $-N(R^8)N-$, $-CON(R^8)-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, or $-N(R^8)SO_2N(R^8)-$,

R^8 is ~~is~~ a hydrogen atom or an optionally substituted C_{1-6}alkyl group,

t is zero or the integer 1,

u is an integer 1, 2 or 3,

Alk^2 is an aliphatic or heteroaliphatic chain, and

R^4 is a hydrogen or halogen atom or a group selected from an optionally substituted C_{1-6}alkyl or C_{3-8} cycloalkyl group, $-OR^5$ (where R^5 is a hydrogen atom, an optionally substituted C_{1-6}alkyl or C_{3-8} cycloalkyl group), $-SR^5$, $-NR^5R^6$ (where R^6 is as just defined for R^5 and may be the same or different), $-NO_2$, -CN, $-CO_2R^5$, $-SO_3H$, $-SOR^5$, SO_2R^5, $-SO_3R^5$, $-OCO_2R^5$, $-CONR^5R^6$, $-OCONR^5R^6$, $-CSNR^5R^6$, $-COR^5$, $-OCOR^5$, $-N(R^5)COR^6$, $-N(R^5)CSR^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)SO_2R^6$, $N(R^5)CON(R^6)(R^7)$ (where R^7 is a hydrogen atom, an optionally substituted C_{1-6}alkyl or C_{3-8}cycloalkyl group), $-N(R^5)CSN(R^6)(R^7)$ or $-N(R^5)SO_2N(R^6)(R^7)$,

provided that when t is zero and each of L^3 and L^4 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom;

L^2 is a covalent bond or an atom or group -O-, -S-, -C(O)-, -C(S)-, -S(O)-, $-S(O)_2$, $-N(R^8)$- or $-C(R^8)(R^{8a})$- (where R^{8a} is an atom or group as defined for R^8 and may be the same or different);

Ar^2 is an optionally substituted aromatic or heteroaromatic group;

Alk is a chain

$-CH_2CH(R)-$, $-CH=C(R)-$, $-\underset{\displaystyle CH_2R}{\overset{\displaystyle |}{CH}}-$ or $-\underset{\displaystyle CHR}{\overset{\displaystyle \|}{C}}-$

in which R is a carboxylic acid ($-CO_2H$), a carboxylic acid ester, a carboxylic acid amide, or a carboxylic acid biostere;

R^1 is a hydrogen atom or a C_{1-6}alkyl group;

L^1 is a covalent bond or a linker atom or group -O-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, $-S(O)_2$-, $-N(R^8)$-, $-N(R^8)O$-, $-N(R^8)N$-, $-CON(R^8)$-, $-OC(O)N(R^8)$-, $-CSN(R^8)$-, $-N(R^8)CO$-, $-N(R^8)C(O)O$-, $-N(R^8)CS$-, $-S(O)_2N(R^8)$-, $-N(R^8)S(O)_2$-, $-N(R^8)CON(R^8)$-, $-N(R^8)CSN(R^8)$-, or $-N(R^8)SO_2N(R^8)$-;

Alk^1 is an optionally substituted aliphatic chain;

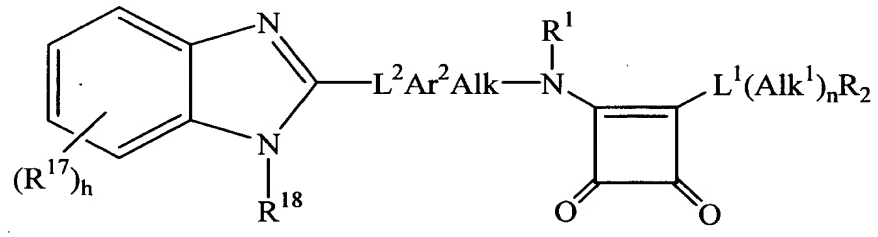
n is zero or the integer 1;

R^2 is a hydrogen atom or an optionally substituted heteroaliphatic, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, C_{3-10}heterocycloalkyl, C_{3-10}heterocycloalkenyl, C_{7-10}bicycloalkyl, C_{7-10}tricycloalkyl, C_{7-10}bicycloalkenyl, C_{7-10}tricycloalkenyl, C_{7-10}bicycloheteroalkyl, C_{7-10}tricycloheteroalkyl, C_{7-10}bicycloheteroalkenyl, C_{7-10}tricycloheteroalkenyl, aromatic or heteroaromatic group, wherein said heteroaliphatic, heterocycloalkyl, heterocycloalkenyl, bicycloheteroalkyl, tricycloheteroalkyl, bicycloheteroalkenyl and tricycloheteroalkenyl groups contain one, two, three, or four heteroatoms or heteroatom-containing groups as defined for L^3 and L^4, which may be the same or different;

provided that Het is not a 2,6-naphthyridin-1-yl, isoquinolin-1-yl, 2,7-naphthyridin-1-yl or quinazolin-4-yl group;

and the salts~~, solvates, hydrates~~ and N-oxides thereof.

15. (Amended Twice) A compound according to Claim 1 of formula (2a):



(2a)

wherein:

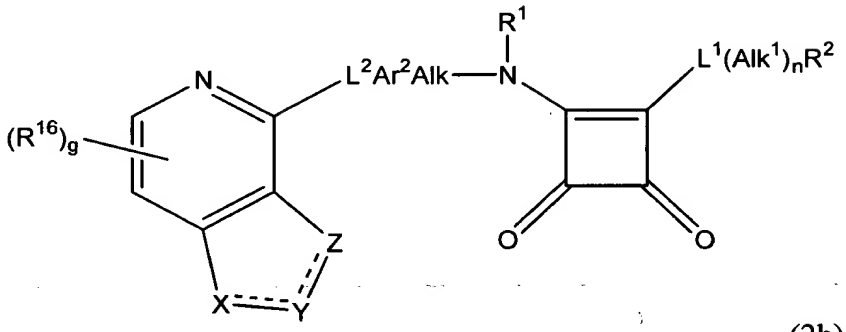
R^{17} is an atom or group R^{16} as previously defined;

h is zero or the integer 1, 2 or 3;

R^{18} is a hydrogen atom or an atom or group R^{16} as previously defined;

and the salts~~, solvates, hydrates~~ and N-oxides thereof.

16. (Amended) A compound according to Claim 1 of formula (2b):



(2b)

wherein:

X, Y and Z ~~is~~ are each independently selected from a nitrogen, oxygen or sulphur atom or CH group;

the broken line (---) represents saturation or unsaturation;

and the salts~~, solvates, hydrates~~ and N-oxides thereof.

19. (Amended Twice) A compound which is:

S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;

S-2-{[2-Dipropylamino)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;

S-2-{[2-(2-Methylpiperidin-1-yl)-3,4-dioxo-1-cyclobutenyl]amino}-3-{4-[(1-methylbenzimidazol-2-yl)amino]phenyl}propanoic acid;

(*S*)-3-[4-(Thiophen[2,3-d]pyrimidin-4-ylamino)phenyl]2-(2-(diethylamino-3, 4-dioxocyclobut-1-enylamino)propanoic acid;

and the salts~~, solvates, hydrates~~, N-oxides and carboxylic acid esters thereof.

21. (Amended Twice) A method for the treatment of inflammatory arthritis, ~~multiple sclerosis,~~ allograft rejection, diabetes, inflammatory dermatoses, asthma or inflammatory bowel disease comprising administering to a mammal suffering from such a disease or disorder a therapeutically effective amount of a compound according to Claim 1.